Decision Memo for Extracorporeal Immunoadsorption Using Protein A Columns for Rheumatoid Arthritis (CAG-00057N)

Decision Summary

Revise the national coverage policy for Extracorporeal Immunoadsorption Using Protein A Columns to include the treatment of Rheumatoid Arthritis

Amend CIM 35-90 to include:

Extracorporeal Immunoadsorption Using Protein A Columns are covered as medically necessary and reasonable for the treatment of rheumatoid arthritis when the following conditions are met:

1. Patient has severe rheumatoid arthritis. Patient disease is active, having > 5 swollen joints, > 20 tender joints, and morning stiffness > 60 minutes.

2. Patient has failed an adequate course of a minimum of 3 DMARDs. Failure does not include intolerance.

Back to Top

Decision Memo

TO: File: CAG - 00057N
Extracorporeal Immunoadsorption Using Protein A Columns for Rheumatoid Arthritis

FROM:

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RE: National Coverage Determination
DATE: April 27, 2000

This memo serves four purposes: (1) outlines the description and treatment of rheumatoid arthritis; (2) reviews the history of Medicare's coverage policies on rheumatoid arthritis; (3) analyzes the relevant scientific data related to the use of a Protein A immunoadsorption column for the treatment of refractory rheumatoid arthritis; and (4) delineates the reasons supporting a positive national decision to cover this therapy for patients with severe rheumatoid arthritis refractory to drug therapy.

Background:

Rheumatoid arthritis (RA) is an inflammatory disorder characterized by a chronic symmetric polyarthritis, multisystemic extraarticular manifestations, and spontaneous exacerbations and remissions of disease activity. The etiology remains unknown, although the cause is felt to be multifactorial with a strong immunological association.

No specific laboratory or radiologic test exists to conclusively diagnose RA. Rather, the diagnosis is based on the presence of at least four of the seven criteria outlined in the American Rheumatism Association's 1987 Revised Criteria for the Classification of Rheumatoid Arthritis.

American Rheumatism Association[1]: 1987 Revised Criteria for the Classification of Rheumatoid Arthritis

1. Morning stiffness lasting at least one hour (minimum 6 weeks)
2. Arthritis of three or more joint areas simultaneously an observed by a physician (minimum 6 weeks)

3. Arthritis of hand joints (minimum 6 weeks)
4. Symmetric arthritis (minimum 6 weeks)
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or adjacent to the involved joint.

The prevalence of RA is 0.5 to 2.0% of the population, with female-to-male ratio of 2.5:1. Typical presentation is a woman in her 20s-50s, with an insidious onset of pain and swelling in the small joints of the hands, wrists, and feet. Although once considered to be a relatively benign disease, RA is now known to result in considerable disability and has a higher-than-expected mortality (up to 10 years shorter than the general population). RA results in more than 9 million physician visits and more than 250,000 hospitalizations annually. While 20% of patients will improve spontaneously or even achieve remission, especially in the first year of disease, chronic disease progression and functional deterioration occur in the majority of patients.

Treatment Options

Currently, no cure for RA exists. Since it is a progressive disease, the therapeutic goals are to reduce pain and swelling by controlling the underlying inflammatory process and to maintain/improve function. Treatment options include physical and occupational therapy, non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying drugs (DMARDs), corticosteroids, and surgery.

Drug therapy

NSAIDs are often the first-line agents. By reducing inflammation through inhibition of prostaglandin synthesis, and providing a degree of analgesia, patients can relieve some of their symptoms. Side effects include gastrointestinal upset and renal insufficiency. With the advent of the cyclooxygenase-2 (COX-2) inhibitors, NSAIDs have received renewed interest as first-line therapy. As with most other drugs, NSAIDs are usually continued until no longer effective or side effects limit further use. However, they do not alter the natural disease process, and thereby do not prevent joint destruction.

DMARDs do have the potential to reduce or prevent joint damage, slowing progression of the disease. They include:

- Hydroxychloroquine (Plaquenil)
- Sulfasalazine (Azulfidine)
- Methotrexate
- Gold therapy (Chrysotherapy)
- Penicillamine
- Cyclophosphamide
- Azathioprine
- Minocycline
- Leflunomide (Arava)

The specific choice of drug depends on co-morbidities, adverse reactions, and convenience of dosing. The newest DMARDs involve the anti-tumor necrosis factor agents (TNF-alpha), Enbrel ® (Etanercept), and Remicade ™ (Infliximab). Etanercept is a soluble recombinant tumor-necrosis factor-alpha receptor, and was initially introduced for patients with severe RA who have failed other disease-modifying agents. (It has recently been approved as first line therapy.) Toxicity appears to be low short-term but concerns about potential oncogenesis or infectious complications from prolonged TNF-alpha blockade remains to be determined. Infliximab, initially approved for treatment of Crohn's disease, also is being selectively used for treatment of RA. The recommended dose of Inflizimab is 3mg/kg infusions every 8 weeks.

Medicare does not currently have a prescription drug benefit, and therefore drug therapy, in general, is not covered under the Medicare program. However, because some drugs (e.g. Infliximab, Gold, Cyclophosphamide, IM Methotrexate) must be administered under the supervision of a physician during an office visit, coverage of such drugs for RA may be determined at the local Medicare carrier level.

Corticosteroids also represent a treatment option for some patients. The use of steroids, in low doses, is usually reserved for patients with aggressive joint disease whose ability to function is compromised, because side effects of steroids such as diabetes, hypertension, and avascular necrosis may ensue.

Surgical Treatment

Surgery is sometimes considered for those patients with chronic RA who remain symptomatic, despite drug therapy, and suffer from joint damage. Symptoms include pain and limited range of motion. For those limited number of patients for whom surgery is an option, typical surgical procedures include carpal tunnel release, and hip/knee arthroplasty.

Protein A Immunoadsorption Column with Plasmapahresis Therapy

This immunoadsorption column is composed of Staphylococcus bacteria-derived Protein A covalently bound to an inert silica matrix. Protein A is a component of certain strains of the Staphylococcus bacterium, which binds immunoglobulin (IgG) as well as circulating immune complexes. Since a cause of RA is believed to be immunologic, the column theoretically works by binding and subsequently remodeling immune complexes. The specific mechanism of action, however, remains unknown.

Prosorba column is a Protein A immunoadsorption treatment column developed by Cypress BioScience, Inc (Cypress) to be used as part of blood aphereis. It was approved by the FDA for the treatment of idiopathic thrombocytopenic purpura (ITP) since 1987. In March 1999, FDA approved its use for moderate to severe RA, in adults with long-standing disease who have failed or are intolerant to DMARDs. Cypress is currently the only manufacturer of the Staph Protein A column.

The treatment regimen for patients with RA differs from the treatment for ITP. Only 1250 ml of plasma are treated for RA patients as opposed to 2000 ml for ITP patients. In addition RA patients are treated once a week for 12 weeks, with each procedure taking approximately 2-3 hours. The number of treatments and intensity of treatments vary for ITP depending upon platelet count.

American College of Rheumatology (ACR) Response Criteria

Over the past decade, an international consensus effort has led to the development of a core set of outcome measures for evaluation of all proposed RA therapies[2]. These outcome measures form the basis of the ACR response criteria, which categorize a patient as a "responder" or "nonresponder". A patient must exhibit a minimum of 20% improvement in both the traditional measures of tender and swollen joint counts, as well as in 3 of the following 5 items to be classified as a responder:

1. Patient Global Assessment as measured with a visual analog scale
2. Physician Global Assessment
3. Physical Disability Score as measured with the Health Assessment Questionnaire (HAQ)
4. Acute-phase reactant (e.g. ESR or C-reactive Protein level)
5. Patient pain assessment with a visual analog scale

This measure of response is termed the ACR20 response.

The American College of Rheumatology has no official position on the specific use of the Protein A column for the treatment of RA. The College does not make any endorsements of specific therapies.

History of the Coverage Process

The Protein A column is covered for idiopathic thrombocytopenic purpura (Coverage Issues Manual [CIM] 35-90), since 1991. All other uses have been considered investigational and therefore not covered.

35-90 EXTRACORPOREAL IMMUNOADSORPTION (ECI) USING PROTEIN A COLUMNS FOR THE TREATMENT OF PATIENTS WITH IDIOPATHIC THROMBOCYTOPENIA PURPURA (ITP) FAILING OTHER TREATMENTS (Effective for services performed on and after 5/6/91)

Extracorporeal immunoadsorption (ECI), using Protein A columns, has been developed for the purpose of selectively removing circulating immune complexes (CIC) and immunoglobulins (IgG) from patients in whom these substances are associated with their diseases. The technique involves pumping the patient's anticoagulated venous blood through a cell separator from which 1-3 liters of plasma are collected and perfused over adsorbent columns, after which the plasma rejoins the separated, unprocessed cells and is retransfused to the patient.

The use of Protein A columns is covered by Medicare only for the treatment of ITP failing other treatments. Other uses of these columns are currently considered to be investigational and, therefore, not reasonable and necessary under the Medicare law. (See §1862(a)(1)(A) of the Act.)

Analysis of Scientific Data

Appendix A gives an overview of the three articles reviewed.

In a prospective, multi-center randomized, double-blinded, placebo-controlled phase III clinical trial[3], Felson et al designed their study for patients with severe and active RA who had failed either methotrexate or 2 or more DMARDs. A 1-3 month washout period where the patient was taken off all DMARDs prior to randomization was required. The following schematic provided by the authors outlines their protocol design:

Patients were randomized to receive either 12 sham procedures (plasmapharesis without the use of the column), or 12 active treatments once a week for 12 weeks. The patient then entered into a follow-up phase for at least an additional 8 weeks. The study protocol did not allow DMARDs use throughout the trial, however, study participants could remain on a stable dose of NSAIDs. A total of 109 patients at 12 sites were randomized. Enrolled patients had an average age of 52.7 years, mean disease duration of 15.5 years and failed a mean of 4.2 DMARD regimens.

Of the 109 patients randomized, 52 were assigned to Prosorba, 47 to sham group, and 10 patients were randomized but switched to an open label study. The primary endpoint compared ACR20 responses at week 19 and 20. If a patient was a responder by ACR criteria, he/she was followed until the time when the response fell below ACR20, or the patient started requesting DMARDs.

The study was originally designed to enroll 268 patients (based on a power calculation of 20% improvement over placebo effect). However, an external data safety monitoring board recommended that the trial be stopped early because a statistical difference between the two treatment groups was noted. Treatment was then offered to all study participants.

By the time the trial halted, 91 patients had completed all 12 treatments and post-treatment evaluations. An additional 8 patients had completed all 12 treatments but had not yet completed all post-treatment evaluation, for a total of 99 patents. An additional 10 patients had initiated treatment but had not yet completed all 12 treatments, for a total of 109 patients. Efficacy results were reported on the 99 patient database.

After trial week 24, all patients classified as either non-responders, or who had responded but subsequently lost their earlier response, were given the opportunity to enter an open-phase trial in which they were guaranteed of receiving treatments with the Prosorba column. Long-term follow-up continued for those patients still responding after trial week 24.

For those patients who completed 12 weeks of therapy and reached the primary effectiveness endpoint at week 19/20, 41.7% (15/36) showed a response to treatment with the Prosorba column vs 15.6 % (5/32) with the placebo ($p<0.003$). For tender joint count, swollen joint count, and patient global assessment, the average responder exceeded 50% improvement. The HAQ score showed 30% improvement. The mean duration of response was 37 weeks, with general response to therapy within 9-13 weeks. Intent-to-treat analysis of all patients indicated 15/2 (28.9%) response rate in the experimental group, as compared to 5/47 (10.6%) response rate among the placebo group ($p=0.005$)

For the open-label, continuation phase, efficacy was evident in 33% of the active-treatment compared with 9% of the sham-treated patients. Moreover, patients with initial responses were more likely to respond to a second course of therapy.

Cypress provided nonpublished information on Medicare patient enrollment in this trial. Of the 109 enrolled patients, 40 patients were Medicare beneficiaries. (20 patients were less than 65 years of age, and qualified for Medicare due to disability). There was no difference in response to treatment between this group of patients and the other patients in the trial.[4]

Adverse events included arthritic flaring, hypotension, nausea/vomiting, rash, arthralgia, fever, and flushing. As a result, the label recommends against the use of central lines and suggests that therapy be discontinued if hemoglobin levels fall below 8g/dL.

Of note, this study was conducted before the introduction of Etanercept. Post-market surveillance by Cypress shows that prior Etanercept use and failure does not predict Prosorba column response rate. This surveillance also demonstrates a consistent Protein A column response rate, regardless of which specific DMARD and/or biologic treatments have been tried and failed.

In the Phase II clinical trial, Caldwell et al embarked on an uncontrolled open-label study of 15 patients at 3 sites. Patients who had failed to respond to two or more DMARDs underwent a washout period of 1 to 3 months prior to enrollment. Average age was 50.4 years with a mean disease duration of 10.9 years. They had an average of 27.8 tender joints, 18.5 swollen joints, and had failed an average of 3.7 DMARDs. Patients were treated with Prosorba column once per week for twelve weeks and then followed for 12 weeks following the last treatment. Researchers performed assessments at weeks 1,2,4,8 and 12 following the last treatment. Improvement in Paulus criteria at 16 weeks post-enrollment was used as the primary endpoint.[5] Nine of 15 patients showed > 20% improvement and 7 of 15 patients showed > 50% improvement in the Paulus criteria.

In the Pilot trial, Wiesenhutter prospectively enrolled 11 patients with RA who failed an average of 4.8 DMARDs. Assessment using Paulus criteria was the primary endpoint. Nine patients met > 50% improvement criteria at week 13, four patients met > 50% improvement criteria at week 24.

Analysis of the Adequacy of the Scientific Evidence Related to Coverage of Extracorporeal Immunoadsorption Using Protein A Columns for Rheumatoid Arthritis

In analyzing the data and considering coverage of the Protein A column for RA, the following questions arise:

- Is the sample size adequate?
- Are the outcomes clinically relevant?
- Are the results durable?
- Who is the appropriate patient population?

Adequacy of sample size is an important consideration in determining effectiveness. The issue of sample size should be evaluated in terms of the power of the study. Power refers to the probability of rejecting the null hypothesis (i.e. no difference exists between the treatment and placebo groups) when it is false. Power is especially important to note for those studies that show no difference in treatment therapies, i.e. a small sample size may not allow enough power to detect a difference that truly exists. Moreover, there is sometimes a tendency to assume that the results of studies with small numbers of patients are not valid. It is important to note that there is no minimum number of patients that can arbitrarily be determined for a study. Rather, one must estimate the effect size to be seen, the error rate (false positive and false negative rates) that will be acceptable, and then calculate the number of patients necessary to show statistical significance.

In the studies related to the Protein A column, the investigators explicitly state their power calculations. The power calculation was based on an estimated response difference of 20% (after adjusting for placebo effect) between Prosorba and sham groups. The error rates employed by the investigators were standard, commonly used rates. Therefore, in analyzing the data, the focus needs to be on the clinical effect, rather than the number of patients in the study. Recognizing that the patients enrolled in these studies suffered from severe RA and had already failed multiple drug regimens, 20% improvement appears to be a reasonable clinical improvement for this patient population. It would be unrealistic to expect that such patients, in general, would demonstrate 50% improvement. Additionally, the criteria which the investigators used, either the Paulus or ACR20 criteria, are the standards which the FDA requires to determine efficacy.

The outcomes measured by the investigators primarily focused on the ACR 20 and/or Paulus criteria. These measures are valid outcomes, and are recognized by the FDA and the ACR. There has been criticism that the studies did not look at radiographic measures, to determine any changes in joint deformities. Again, this patient population already has significant joint damage, and it may be difficult to see subtle radiographic changes. As a result, radiological changes are not the preferred clinical outcome. Other therapies (e.g. drugs) for RA also used percentage improvement in ACR response criteria as their primary endpoint.

The durability of results also needs to be considered in analyzing the data. Phase III trial participants demonstrated a response up to 37 weeks, with a range of 20-84 weeks. In recent drug trials, Infliximab investigators assessed ACR 50 at 30 weeks and Etanercept researchers determined response at 6 months, with open-label responses up to 18 months. It is important to note, however, that drug treatment and plasmapharesis are vastly different types of therapies. The response to drug treatment continues only as long as the patient takes the drug, whereas the response to the Protein A column maintains durability several months following therapy. The results reported in these studies are as durable as those measured in other RA treatment studies.

The appropriate patient population can be gleaned from the study populations. The three studies focused exclusively on those patients with severe RA who have failed multiple DMARDs. For most patients, this therapy was a last resort, prior to possible surgical intervention. The studies did not examine the effects of plasmapharesis using Protein A columns for patients with moderate disease, and therefore determination of the appropriateness of this treatment for such patients is presently unknown. Given the intensity of this treatment and the lack of knowledge concerning its mechanism of action, we do not believe that the results of the studies can be generalized to patients with more moderate disease.

Conclusion

In conclusion, HCFA’s analysis of the data suggests that extracorporeal immunoadsorption using Protein A column is a reasonable and necessary treatment for rheumatoid arthritis. Based on the data, coverage should be limited to patients with severe rheumatoid arthritis who have failed a minimum of 3 DMARDS.

DECISION:

Revise the national coverage policy for Extracorporeal Immunoadsorption Using Protein A Columns to include the treatment of Rheumatoid Arthritis

Amend CIM 35-90 to include:

Extracorporeal Immunoadsorption Using Protein A Columns are covered as medically necessary and reasonable for the treatment of rheumatoid arthritis when the following conditions are met:

1. Patient has severe rheumatoid arthritis. Patient disease is active, having > 5 swollen joints, > 20 tender joints, and morning stiffness > 60 minutes.

2. Patient has failed an adequate course of a minimum of 3 DMARDs. Failure does not include intolerance.

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[1] Now known as the American College of Rheumatology (ACR)

[2] Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology preliminary definitions of improvement in rheumatoid arthritis. Arthritis & Rheumatism 38:727-735, 1995.

[3] Phase I trials attempt to identify the maximum tolerated dose of a drug or biologic, or the conditions for using a device. Phase II trials are designed to screen for possible biologic effectiveness and identify side effects or toxicity rates. Phase III trials are the comparative trials, designed to test the effectiveness of a therapy and estimate the cost-benefit ratio. Phase IV trials typically are long-term follow-up studies to scrutinize approved or accepted therapies for potential harm not observed in the Phase III trial.

[4] Investigators provided summary data, with an intent-to-treat analysis.

[5] Paulus criteria include: morning stiffness, Westergren ESR, joint pain/joint score, patients/physicians overall assessments of current disease activity.

Back to Top

Bibliography

American College of Rheumatology. Guidelines for monitoring drug therapy in rheumatoid arthritis. *Arthritis and Rheumatism* 1996; 39:722-731.

American College of Rheumatology. Guidelines for management of rheumatoid arthritis. *Arthritis and Rheumatism* 1996; 39:713-722.

Anderson JJ, Wells G, et al. Factors predicting response to treatment in rheumatoid arthritis. *Arthritis and Rheumatism* 2000; 43:22-29.

Caldwell J, Gendreau RM, and Furst D. A pilot study using a staph protein A column (Prosorba) to treat refractory rheumatoid arthritis. *The Journal Of Rheumatology* 1999; 26:1657-1662.

Felson D, Anderson JJ, Boers, M et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis and Rheumatism* 1993; 36:729-740.

Felson DT, Anderson JJ, Boers M et al. American College of Rheumatology Preliminary Definition of Improvement in Rheumatoid Arthritis. *Arthritis and Rheumatism* 1995; 6:727-735.

Felson DT, Anderson JJ, Lange MM, et al. Should improvement in rheumatoid arthritis clinical trial be defined as fifty percent improvement or seventy percent improvement in core set measures, rather than 20 percent?. *Arthritis and Rheumatism* 1998; 41:156-1570.

Felson DT, LaValley MP, Baldassare AR, Block JA, et al. The Prosorba column for treatment of refractory rheumatoid arthritis. *Arthritis and Rheumatism* 1999; 42:2153-2159.

Paulus HE. Egger MJ, Ward JR, et al. Analysis of improvement in individual rheumatoid arthritis patients treated with disease modifying anti-rheumatic drugs, based on the findings in patients treated with placebo?. *Arthritis and Rheumatism* 1990; 33:477-484.

Strand V. Recent advances in the treatment of rheumatoid arthritis. *Clinical Cornerstone* 2000; 2:36-50.

Wiesenhutter CW, Irish BL, and Bertram JH. Treatment of patients with refractory rheumatoid arthritis with extracorporeal protein A Immunoadsorption columns: a pilot trial. *The Journal of Rheumatology* 1994; 21:804-810.

Back to Top

Related Material

Literature Review
Back to Top